PATENT SPECIFICATION

505,983

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PROVISIONAL SPECIFICATION
No. 31629 A.D. 1937.

Improvements in the Manufacture and Production of Pharmaceutically Active Substances

I, GEORGE WILLIAM JOHNSON, a British Subject, of 47, Lincoln's Inn Fields, in the County of London, Gentleman, do hereby declare the nature of this invention (which has been communicated to me from abroad by I. G. Farbenindustrie Aktiengesellschaft, of Frankfort-on-Main, Germany, a Joint Stock Company organised under the Laws of Germany), to be as follows:—

My foreign correspondents have found that pharmaceutically active substances which are usually diluted with water or aqueous media before use can be obtained in a stable, homogeneously dilutable form as such or in the form of clear solutions by adding thereto water soluble phosphatides.

It is of special advantage to employ the addition of the said phosphatides in the case of drug extracts. The phosphatide may be added for example to the drug to be extracted whereby, for example in the recovery of valerian extract, generally speaking considerably better yields of pharmacologically active substances are obtained than without the said addition. On the other hand the phosphatides may be added to the extraction agent, as for example alcohol or ether, before or during the extraction. Finally the phosphatides may be added to the finished extracts or extract solutions.

With the drug extracts obtainable in the said manner there may be mixed without objection additional amounts of the active substance contained in the drug or other desirable additional substances, as for example substances improving taste, such as peppermint oil and the like.

In the said manner it is possible for example to obtain extracts of sage, camomile, peppermint, valerian and other plants esteemed as medicaments, in particular those containing ethereal oils, which have considerable advantages over the decoctions hitherto usual. Whereas the preparation of decoctions is always troublesome and does not permit of accurate dosage by reason of the varying composition of the drugs and the different methods of preparing the decoctions, the use and simultaneous dosage of solutions to which phosphatides have been added is very simple.

The extracts prepared according to this invention may be stored for any length of time as such or in the form of more or less concentrated solutions. Upon dilution with water before use, no separation of insoluble constituents takes place either in the cold or hot; such separation may readily take place in the case of extracts prepared without the addition of phosphatides when they are diluted. The extracts obtainable according to this invention have a beautiful colour which does not change.

Ethereal oils, as for example chenopodium oil, and also carbon tetrachloride, which may be used dispersed in water as an anti-helminthic, and similar pharmaceutically active substances may also be brought into a form in which they are homogeneously dilutable with water by the addition of phosphatides.

The amount of phosphatide depends on the pharmaceutically active substance, on the nature of the phosphatide and on the effect intended. Water soluble phosphatides are especially suitable which have no pronounced taste and of which only a small amount suffices to produce solutions, as for example alcoholic solutions, of ethereal oils which are capable of dilution with water to give clear solutions. Lysolecithin is a watersoluble phosphatide which may be used with special advantage.

Basic substances, as for example alkali hydroxides, alkali carbonates, ammonia or organic amines may also be added to the new extracts in known manner. Usually it is sufficient to use smaller amounts of phosphatide and basic substances than are necessary for the production of homo-

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geneously dilutable substances by th sole use of phosphatides or basic substances.

The substances provided with the addition of the said phosphatides may also be used in undiluted form, as for example as alcoholic solutions for painting or in the form of powder for dusting.

The following Examples will further illustrate the nature of this invention but the invention is not restricted to these Examples. The parts are by weight, unless otherwise specified.

EXAMPLE 1.

10 parts of dry sage crude extract are shaken for some hours at room temperature with 80 parts of a 3 per cent. alcoholic solution of lysolecithin. After allowing to stand for several hours, the resulting solution is freed from the constituents which have settled to the bottom, for example by siphoning off, and if necessary filtered. If 1 cubic centimetre of the extract be diluted with 100 cubic centimetres of drinking water, a clear, greenish yellow solution of pleasant odour and taste is obtained which is free from deposits.

On the contrary an alcoholic solution prepared under otherwise identical conditions but without the use of the phosphatide, yields immediately by dilution with water a flocculent precipitate and the separated constituents form an upper floating layer.

EXAMPLE 2.

1 part by volume of sage oil or carbon tetrachlorid is dissolved in 2 parts by volume of a 7.5 per cent. alcoholic solution of lysolecithin. By adding 1 cubic centimetre of this solution to 100 cubic centimetres of drinking water, there is obtained a homogeneous, milky, finely dispersed emulsion, whereas when working without the use of phosphatide immediate separation of sage oil or carbon tetrachloride takes place.

EXAMPLE 3.

50 parts of valerian crude extract (obtained by the extraction of valerian root with alcohol) are extracted hot with 120 parts of a 4.5 per cent. alcoholic solution of lysolecithin. The concentrated solution obtained by filtration after cooling yields by dilution with drinking water in the ratio 1:100 a brownish, homogeneous solution which shews not the slightest deposition even after standing for 24 hours. A similar extract obtained without the use of lysolecithin, however, deposits large amounts of solid constituents and contains less active substances than that obtained with lysolecithin.

Dated this 17th day of November, 1937.

J. Y. & G. W. JOHNSON,
47, Lincoln's Inn Fields, London, W.C.2,
Agents.

PROVISIONAL SPECIFICATION
No. 33197 A.D. 1938.

Improvements in Water-soluble or Emulsifiable Preparations comprising Organic Substances

I, GEORGE WILLIAM JOHNSON, a British Subject, of 47, Lincoln's Inn Fields, in the County of London, Gentleman, do hereby declare the nature of this invention (which has been communicated to me from abroad by I. G. Farbenindustrie Aktiengesellschaft, of Frankfort-on-Main, Germany, a Joint Stock Company organised under the Laws of Germany), to be as follows:—

In the specification No. 31629 A.D. 1937 there is described a process for producing pharmaceutically active substances which are usually diluted with water or aqueous media before use in a stable homogeneously dilutable form as such or in the form of clear solutions by adding thereto water-soluble phosphatides.

My foreign correspondents have now found that not only pharmaceutically active substances but generally speaking organic substances which are difficultly solubl in water, but soluble in organic solvents can be brought into the form of stable emulsions which are homogeneously dilutable with water to form substantially clear emulsions or solutions by the addition of water-soluble phosphatides. As substances which can thus be brought into homogeneously dilutable form there may be mentioned resins, oils, fats, sterines, waxes, fatty acids, high molecular hydrocarbons and the like. The emulsions obtainable from the said substances are suitable for many industrial purposes.

As suitable water-soluble phosphatides there may be mentioned lysolecithin, lysocephalin and synthetic products of analogous constitution. Synthetic products having a constitution analogous to that of lysolecithin and lysocephalin may be prepared by introducing by means of phosphorus oxychloride a phosphoric acid radicle into a mono fatty acid ester of glycerine and esterifying the phosphoric acid radicle with choline, colamine or similar amines.

The following Examples will further

illustrate th nature of this invention but the invention is not restricted to these Examples. The parts are by weight.

EXAMPLE 1.

50 parts of artemisia absynthium ar extracted hot with 120 parts of 4 per cent. alcoholic solution of lysolecithin. The concentrated solution obtained by filtration after cooling yields by dilution with drinking water in the ratio 1:100 a brownish, homogeneous solution which shews not the slightest deposition even after standing for 24 hours. The solution may be employed with advantage in the production of wines and liqueurs (vermouth).

A similar extract obtained without the use of lysolecithin, however, deposits large amounts of solid constituents and contains less active substances than that obtained with lysolecithin.

EXAMPLE 2.

A 4.5 per cent. alcoholic solution of lysolecithin is saturated in the cold or hot with a sterine or a sterine derivative. When the solution obtained is poured into 100 times its volume of water a stable homogeneous emulsion of a very high degree of dispersion is produced.

By way of comparison it may be stated that an analogous solution which does not contain lysolecithin when poured into water leads to immediate separation of the sterine or sterine derivativ which forms a layer on the surfac of the water.

EXAMPLE 3.

1 part by weight of a fatty acid triglyceride of oily consistency, for example oleic acid triglyceride, is dissolved in 3 parts by weight of a 5 per cent. alcoholic solution of lysolecithin or a synthetic phosphatide of analogous constitution.

If one cubic centimetre of this solution is poured into 50 cubic centimetres of water a homogeneous emulsion of the triglyceride is obtained which may be employed for cosmetic purposes, for the treatment of leather and the like.

If lysolecithin or the synthetic phosphatide is not co-employed an emulsion of the said kind cannot be obtained.

Dated this 15th day of November, 1938.

J. Y. & G. W. JOHNSON,
47, Lincoln's Inn Fields, London, W.C.2,
Agents.

COMPLETE SPECIFICATION

Improvements in Water-soluble or Emulsifiable Preparations comprising Organic Substances

I, GEORGE WILLIAM JOHNSON, a British Subject, of 47, Lincoln's Inn Fields, in the County of London, Gentleman, do hereby declare the nature of this invention (which has been communicated to me from abroad by I. G. Farbenindustrie Aktiengesellschaft, of Frankfort-on-Main, Germany, a Joint Stock Company organised under the Laws of Germany), and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

My foreign correspondents have found that preparations comprising organic substances which are difficultly soluble in water, but readily soluble in organic solvents (such as vegetable extracts obtained by means of organic solvents and which are usually diluted with aqueous media before use, furthermore essential oils, resins, fats, sterols, waxes, fatty acids, high molecular hydrocarbons and the like) which preparations are stable and homogeneously dilutable with water or aqueous media to form substantially clear emulsions or solutions can be obtained by adding watersoluble phosphatides to the said organic substances.

It is of special advantage to employ the addition of the watersoluble phosphatides in the case of vegetable extracts. The said phosphatides may be added for example to the plant to be extracted, whereby, generally speaking considerably better yields of extracts are obtained than without the said addition. On the other hand the said phosphatides may be added to the extraction agents, as for example alcohol, before or during the extraction. Finally the watersoluble phosphatides may be added to the finished extracts or extract solutions.

With the extracts obtainable in the said manner there may be mixed without objection additional amounts of the active substance contained in the plant or other desirable additional substances, as for example substances improving taste, such as peppermint oil and the like.

In the said manner it is possible for example to obtain extracts of camomile, peppermint, wormwood, juniper and other plants containing essential oils and esteemed in the production of essences for the preparation of liqueurs, wines, cosmetic preparations and additions to baths. A most valuable technical advantage of

the new process consists in the fact that the products prepared may be stored for any length f tim as such or in the form of more or less concentrated solutions. Upon dilution with water or aqueous solutions no separation of insoluble constituents takes place either in the cold or hot; such separation may readily take place in the case of products prepared without the addition of the said phosphatides when they are diluted. Extracts obtainable according to this invention have a beautiful colour which does not change.

Essential oils, carbon tetrachloride and like substances may also be brought into a form in which they are homogeneously dilutable with water by the addition of watersoluble phosphatides. Fats, waxes, resins, sterols, hydrocarbons and like substances may also be brought into a readily emulsifiable form by the addition of watersoluble phosphatides. The emulsions obtainable from the said substances are suitable for many industrial purposes.

The amount of the watersoluble phosphatide depends on the nature of the phosphatide and of the substance to be emulsified and on the effect intended. Such watersoluble phosphatides obtainable from natural phosphatides are especially suitable as have no pronounced taste; small amounts thereof are often sufficient to produce solutions, as for example alcoholic solutions, of essential oils which are capable of dilution with water to give nearly clear emulsions. Lysolecithin and lysocephalin and synthetic products of analogous constitution may be mentioned as most suitable watersoluble phosphatides. They may be employed together with other phosphatides such as lecithin. Synthetic products having a constitution analogous to that of lysolecithin and lysocephalin may be prepared by introducing by means of phosphorus oxychloride a phosphoric acid radicle into a mono fatty acid ester of glycerine and esterifying the phosphoric acid radicle with choline, colamine or similar amines.

Basic substances, as for example alkali hydroxides, alkali carbonates, ammonia or organic amines may also be added to the new products. In this case it is usually sufficient to use smaller amounts of phosphatides and basic substances than are necessary for the production of homogeneously dilutable substances by the sole use of phosphatides or basic substances.

The substances provided with the addition of phosphatides may also be used in undiluted form, as for example as alcoholic solutions for brushing or in the form of powder for dusting.

Th following Examples will further illustrate how the said invention may be carried out in practice but the invention is not restricted to these Examples. The parts are by weight, unless otherwise specified.

EXAMPLE 1.

10 parts of dry sage crude extract are shaken for some hours at room temperature with 80 parts of a 3 per cent. alcoholic solution of lysolecithin. After allowing to stand for several hours, the resulting solution is freed from the constituents which have settled to the bottom, for example by siphoning off, and if necessary filtered. If 1 cubic centimetre of the extract be diluted with 100 cubic centimetres of drinking water, a practically clear, greenish yellow solution of pleasant odour and taste is obtained which is free from deposits.

On the contrary an alcoholic solution prepared under otherwise identical conditions but without the use of the phosphatide, yields immediately by dilution with water a flocculent precipitate and the separated constituents form an upper floating layer.

EXAMPLE 2.

1 part by volume of sage oil or carbon tetrachloride is dissolved in 2 parts by volume of a 7.5 per cent. alcoholic solution of lysolecithin. By adding 1 cubic centimetre of this solution to 100 cubic centimetres of drinking water, there is obtained a homogeneous, milky, finely dispersed emulsion, whereas when working without the use of phosphatide immediate separation of sage oil or carbon tetrachloride takes place.

EXAMPLE 3.

50 parts of valerian crude extract (obtained by the extraction of valerian root with alcohol) are extracted hot with 120 parts of a 4.5 per cent. alcoholic solution of lysolecithin. The concentrated solution obtained by filtration after cooling yields by dilution with drinking water in the ratio 1:100 a brownish, homogeneous solution which shews not the slightest deposition even after standing for 24 hours. A similar extract obtained without the use of lysolecithin, however, deposits large amounts of solid constituents and contains less active substances than that obtained with lysolecithin.

EXAMPLE 4.

1 part by volume of chenopodium oil is dissolved in 3 parts by volume of an alcoholic solution containing 5 per cent. of lecithin and 0.5 per cent. of lysolecithin. By adding 1 cubic centimetre of the solution thus obtained to 100 cubic centimetres of drinking-water a homogeneous emulsion of a very high degree of

dispersion is obtained; if an alcoholic solution free from lecithin and lysolecithin is employed, the chenopodium oil separates at once, a stable emulsion not being formed.

EXAMPLE 5.

1000 parts of dried elder flowers are mixed with 8000 parts of a 4 per cent. alcoholic solution of lysolecithin and allowed to stand for some hours, the whole being shaken from time to time. The mass is then heated to boiling for about 10 minutes and filtered; the filtrate contains 1.59 per cent. of extracted parts. If alcohol alone be employed for the extraction instead of the alcoholic lysolecithin solution, the filtrate contains only 0.72 per cent. of extracted parts.

If sage leaves are extracted in an analogous manner with an alcoholic lysolecithin solution, the filtrate obtained contains 1.75 per cent. of extracted parts while with the employment of alcohol alone the filtrate contains only 1.2 per cent. of extracted parts.

EXAMPLE 6.

50 parts of artemisia absynthium are extracted hot with 120 parts of 4 per cent. alcoholic solution of lysolecithin. The concentrated solution obtained by filtration after cooling yields by dilution with drinking water in the ratio 1:100 a brownish, homogeneous solution which shews not the slightest deposition even after standing for 24 hours. The solution may be employed with advantage in the production of wines and liqueurs (vermouth).

A similar extract obtained without the use of lysolecithin, however, deposits large amounts of solid constituents and contains less active substances than that obtained with lysolecithin.

EXAMPLE 7.

A 4.5 per cent. alcoholic solution of lysolecithin is saturated in the cold or hot with a sterol or a sterol derivative. When the solution obtained is poured into 100 times is volume of water a stable homogeneous emulsion of a very high degree of dispersion is produced.

By way of comparison it may be stated that an analogous solution which does not contain lysolecithin when poured into water leads to immediate separation of the sterol or sterol derivative which forms a layer on the surface of the water.

EXAMPLE 8.

1 part by weight of a fatty acid triglyceride of oily consistency, for example oleic acid triglyceride, is dissolved in 3 parts by weight of a 5 per cent. alcoholic solution of lysolecithin or a synthetic phosphatide of analogous constitution. If one cubic centimetre of this solution is poured into 50 cubic centimetres of water a homogeneous emulsion of the triglyceride is obtained which may be employed for cosmetic purposes, for th treatment of leather and the like.

If lysolecithin or the synthetic phosphatide is not co-employed an emulsion of the said kind cannot be obtained.

I am aware that in Specification No. 417,715 there is described a process for the manufacture and production of pharmaceutical preparations for injection by incorporating pharmaceutically active substances with aqueous emulsions of lipoids, antiseptics, regulators and stabilisers, all being separate substances. I am further aware that in the said Specification there is described the preparation of a mixture by first making an emulsion from 20 parts of myricin, 25 parts of olive oil, 1.0 part of novocain, 0.2 part of the product sold under the name "Nipasol" or the product sold under the name "Nipagin M", 1.5 part of sodium oleate in 9 parts of water, and a second emulsion from 1.5 parts of egglecithin, 9.0 parts of water and 1.0 part of lysolecithin and mixing the two emulsions carefully. The mixture thus obtained is not homogeneously dilutable with water or aqueous media to form substantially clear solutions or emulsions. The lysolecithin is employed with the object of acting as a therapeutic substance in case of rheumatism, lumbago and the like. I make no claim to the coemployment of lysolecithin and lecithin in the production of preparations except in such proportions as will effect the objects I have in view.

Having now particularly described and ascertained the nature of my said invention and in what manner the same is to be performed, I declare that what I claim is:—

1. A process for the manufacture and production of preparations comprising organic substances which are difficultly soluble in water, but soluble in organic solvents, which preparations are stable and homogeneously dilutable with water or aqueous media to form substantially clear emulsions or solutions, which consists in adding watersoluble phosphatides to the said organic substances.

2. In the process as claimed in Claim 1, employing lysolecithin as a watersoluble phosphatide.

3. The process for the manufacture and production of preparations comprising organic substances substantially as described in each of the foregoing Examples.

4. Stable and homogeneously dilutable preparations comprising organic substances, when obtained according to the

process particularly described and ascertained or its obvious chemical equivalents.

Dated this 16th day f November, 1938.
J. Y. & G. W. JOHNSON,
47, Lincoln's Inn Fields, London, W.C.2,
Agents.

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